BETA-CARBOLINE DRUG PRODUCTS

CROSS-REFERENCE TO RELATED APPLICATION

This is the U.S. national phase application of International Application No. PCT/US00/20981, filed on Aug. 1, 2000, which claims the benefit of provisional patent application Ser. No. 60/147,048, filed Aug. 3, 1999.

FIELD OF THE INVENTION

The present invention relates to the fields of pharmaceutical and organic chemistry, and to a β-carboline compound which is useful for the treatment of various medical indications where inhibition of type 5 cGMP-specific phosphodiesterase (PDE5) is desired. More particularly the present invention provides a free drug form of β-carboline particles in a size range allowing for uniform formulation of stable pharmaceutical compositions, especially compositions providing desired bioavailability properties heretofore not provided in the art.

BACKGROUND OF THE INVENTION

The biochemical, physiological, and clinical effects of cyclic guanosine 3',5'-monophosphate specific phosphodiesterase (cGMP-specific PDE) inhibitors suggest their utility in a variety of disease states in which modulation of smooth muscle, renal, hemostatic, inflammatory, and/or endocrine function is desired. Type 5 cGMP-specific phosphodiesterase (PDE5) is the major cGMP hydrolyzing enzyme in vascular smooth muscle, and its expression in penile corpus cavernosum has been reported (Taher et al., J. Urol., 149:285A (1993)). Thus, PDE5 is an attractive target in the treatment of sexual dysfunction (Murray, DN&P 6(3): 150–156 (1993)).

Daugan U.S. Pat. No. 5,859,006 discloses a class of β-carboline compounds, and pharmaceutical compositions containing the β-carbolines, which are useful in the treatment of conditions wherein inhibition of PDE5 is desired. PCT publication WO 97/03675 discloses use of this class of β-carboline compounds in the treatment of sexual dysfunction.

The poor solubility of many β-carboline compounds useful as PDE5 inhibitors prompted the development of coprecipitate preparations, as disclosed in PCT publication WO 96/38131 and Butler U.S. Pat. No. 5,985,326. Briefly, coprecipitates of a β-carboline with polymeric hydroxypropylmethylcellulose phthalate, for example, were prepared, milled, mixed with excipients, and compressed into tablets for oral administration. Studies revealed, however, that difficulties arose in generating precisely reproducible lots of coprecipitate product, which makes use of coprecipitates less than ideal in pharmaceutical formulations.

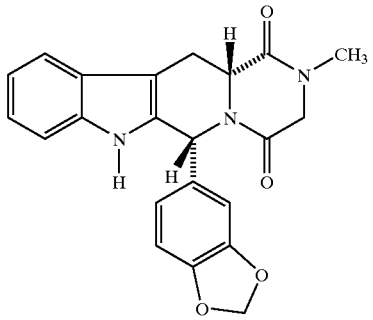
Additionally, clinical studies involving administration of coprecipitate tablets preliminarily revealed that maximum blood concentration of the β-carboline compound is achieved in 3 to 4 hours, with the average time for onset of therapeutic effect not yet precisely determined. In the treatment of sexual dysfunction, such as male erectile dysfunction or female sexual arousal disorder, however, a more rapid achievement of maximum blood concentration, along with a greater prospect for rapid onset of therapeutic effect, frequently is sought by individuals desiring more immediate and/or less prolonged effects. Accordingly, a need in the art continues to exist for orally administrable β-carboline compounds and 5-carboline-containing pharmaceutical compositions having an ability to provide a therapeutic effect within a desirable, or at least acceptable, time frame.

SUMMARY OF THE INVENTION

The present invention provides particulate preparations of a free drug form of a β-carboline compound having specific and defined particle size characteristics. The defined particle size permits a uniform formulation of stable pharmaceutical compositions. In particular, the present invention provides compositions that exhibit a rapid achievement of maximum blood concentration of PDE5 inhibitor and/or a rapid onset of a therapeutic PDE5 inhibitory effect.

The present invention provides a compound having the formula (I)

(I)



and pharmaceutically acceptable salts and solvates thereof, wherein the compound is a free drug in particulate form, and wherein at least 90% of the particles have a particle size of less than about 40 microns, and preferably less than 30 microns. Highly preferred particulate forms of the β-carboline compound (I) have at least 90% of the particles less than 25 microns in size. Most preferred forms of the free compound (I) are those wherein 90% of the particles are less than 10 microns in size.

The present invention provides, therefore, a free form of a β-carboline compound, and compositions containing the β-carboline compound, which can be used in an effective therapy for conditions wherein inhibition of PDE5 provides a benefit. The free form of β-carboline compound (I) has a particle size such that the onset of beneficial effects of PDE5 inhibition are exhibited in a relatively short time after oral administration.

The present invention further relates to pharmaceutical compositions comprising the particulate compound (I) and one or more pharmaceutically acceptable carriers, diluents, or excipients. The invention further provides the use of compound (I) and pharmaceutical compositions for treatment of sexual dysfunction, e.g., male erectile dysfunction and female sexual arousal disorder.

Alternatively stated, the present invention provides for the use of the above-described particulate forms of compound (I) for the manufacture of medicaments for the treatment of sexual dysfunction Specific conditions that can be treated by the compound and compositions of the present invention include, but are not limited to, male erectile dysfunction and female sexual dysfunction, for example, female arousal disorder, also known as female sexual arousal disorder.

Accordingly, one aspect of the present invention is to provide a free drug particulate form of a compound (I), and pharmaceutically acceptable salts and solvates thereof, comprising particles of the compound wherein at least 90% of the particles have a particle size of less than about 40 microns.